Neuroendocrine Host Factors and Inflammatory Disease Susceptibility

Sophie Ligier and Esther M. Sternberg

Clinical Neuroendocrinology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland USA

The etiology of autoimmune diseases is multifactorial, resulting from a combination of genetically predetermined host characteristics and environmental exposures. As the term autoimmune implies, immune dysfunction and dysregulated self-tolerance are key elements in the pathophysiology of all these diseases. The neuroendocrine and sympathetic nervous systems are increasingly recognized as modulators of the immune response at the levels of both early inflammation and specific immunity. As such, alterations in their response represent a potential mechanism by which pathologic autoimmunity may develop. Animal models of autoimmune diseases show pre-existing changes in neuroendocrine responses to a variety of stimuli, and both animal and human studies have shown altered stress responses in the setting of active immune activation. The potential role of the neuroendocrine system in linking environmental exposures and autoimmune diseases is 2-fold. First, it may represent a direct target for toxic compounds. Second, its inadequate function may result in the inappropriate response of the immune system to an environmental agent with immunogenic properties. This article reviews the relationship between autoimmune diseases and the neuroendocrine system and discusses the difficulties and pitfalls of investigating a physiologic response that is sensitive to such a multiplicity of environmental exposures. *Key words*: autoimmunity, eosinophilia myalgia syndrome, Fischer rats, hypothalamic–pituitary–adrenal axis, Lewis rats inflammation, neuroendocrine system, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus. — *Environ Health Perspect* 107(suppl 5):701–707 (1999).
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It is increasingly recognized that autoimmune diseases have a multifactorial etiology. Although genetic studies have identified several susceptibility loci in a variety of inflammatory disorders (*1*), twin studies in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), for example, have at best shown concordance rates between 15 and 30% (*2,3*). This underscores the need for better understanding of the environmental factors involved in triggering autoimmune diseases.

These diseases, although clinically very diverse, are generally believed to result from immune dysregulation and in particular breakdown of self-tolerance. The immune response is regulated through a number of mechanisms, each of which, if altered, could result in the development of disease. Neuroendocrine and sympathetic nervous system responses also play a role in such modulation of host immune responses to antigenic exposure. Although this is a relatively new area of scientific interest, the potential role played by the neuroendocrine system in autoimmunity has been considered since the 1940s. The finding of initially remarkable therapeutic effects with glucocorticoids in RA early on raised the issue of adrenal hormone insufficiency and of hypothalamic–pituitary–adrenal (HPA) axis dysfunction as an etiologic factor of the disease (*4*). More recently, evidence in both human autoimmune processes and in their animal models has been gathered to support the role of the neuroendocrine system in the development of autoimmunity.

The neuroendocrine system becomes particularly relevant when discussing the impact of the environment on the immune system and the susceptibility to autoimmune processes. Indeed, in addition to affecting the immune system at several levels, neuroendocrine activation occurs in response to a wide range of stimuli. Although the term environmental exposure classically designates exposure to potential toxic chemicals or infectious agents, triggers of the neuroendocrine response are very diverse. A wide variety of physical and psychologic stimuli can activate both the neuroendocrine and sympathetic nervous systems, eliciting a cascade of events collectively referred to as the stress response (*5*). The immediate and chronic changes that this sequence of physiologic reactions provokes help the organism cope with the environmental challenges. Conversely, a relative imbalance of the hormonal stress response to an environmental exposure may represent a contributing factor in the development of inflammatory and autoimmune disease. Sex hormones, prolactin secretion, and peripheral neural activation are all additional modulators of the body's response to antigenic stimuli. The development of an autoimmune process is thus likely the result of a critical exposure to environmental factors combined with multiple host susceptibility characteristics, including neuroendocrine responsiveness. Evidence in animal models and human disease indicates that both the neuroendocrine system and putative environmental (often infectious) triggers play a key role in the pathophysiology of several autoimmune diseases. These include RA, SLE, multiple sclerosis (MS), and Sjögren syndrome.

In this article, before summarizing the data implicating the neuroendocrine system in the pathophysiology of autoimmunity, we will first review some concepts on neuroendocrine activation and its effects on the organism.

The Stress Response

Following exposure to a stressful stimulus, sympathetic nervous system activation causes increases in heart rate, sweating, and muscle blood flow. Production of central corticotropin-releasing hormone (CRH) and activation of the locus coeruleus result in behavioral changes such as increased focused attention. Acutely, these behavioral and physiologic responses are collectively referred to as the fight-or-flight response. The HPA axis is quickly activated within minutes after exposure to a variety of stressors, either primarily psychologic (performance tasks), or physical in nature (exercise, trauma, or thermal, chemical/infectious/immune). The hypothalamus secretes the neurohormones CRH and arginine vasopressin, which then signal the pituitary gland to produce corticotropin (ACTH). ACTH in turn stimulates adrenal gland glucocorticoid production. In addition to effects on multiple organ systems including immune cells, glucocorticoids feed back on and suppress the HPA axis cascade at every level.

Stressful stimuli also activate the brain stem, resulting in an increased sympathetic nervous system outflow to the periphery (*6*). Hypothalamic CRH can stimulate brain stem noradrenergic regions and increase their sympathetic activation. In turn, brain stem adrenergic outflow can further signal the hypothalamus to secrete CRH.

The resulting stress response varies depending on the stimulus to which it is exposed. Not surprisingly, the response to psychologic stressors is dependent on the

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Address correspondence to E.M. Sternberg, Section on Neuroendocrine Immunology and Behavior, Clinical Neuroendocrinology Branch, National Institute of Mental Health/NIH, Bldg. 10, Rm. 2D-46, 10 Center Dr., MSC 1284, Bethesda, MD 20892-1284. Telephone: (301) 402-2773. Fax: (301) 402-1561. E-mail: ems@codon.nih.gov

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individual's subjective perception of the event (*7*). Within the category of primarily physical stressors, the HPA axis response differs from one stimulus to another. Intermittent electrical foot shock in rats activates different stress-responsive central nervous system neurotransmitter pathways than a systemic interleukin (IL)-1 challenge (*8*). Similarly, hemorrhage, insulin injection, subcutaneous formaldehyde injection, exposure to cold, and immobilization will all elicit different patterns of epinephrine and ACTH secretion (*9*). The nature, route of exposure, and duration of the immune challenge also determine the HPA axis response pattern (*10*).

The duration of any stressful stimulus is an important determinant of the resulting HPA axis response. Though it is not uniform in all rat species, ACTH secretion control shifts from CRH to arginine vasopressin (AVP) in the presence of chronic inflammatory stress (*11*). This may be due to differential sensitivity of CRH and AVP secretion to negative feedback by corticosterone. Thus, hypothalamic paraventricular nucleus glucocorticoid receptor (GR) mRNA decreases following repeated acute stress (*12*). Similar patterns have been demonstrated in human chronic conditions such as MS. Patients with MS have baseline hypercortisolemia, a blunted ACTH response to AVP, and a normal ACTH response to CRH. Of note, subjects in this study did not exhibit signs of increased peripheral inflammation, e.g., plasma sedimentation rates, IL-6, and IL-1β levels were not increased (*13*). However, these studies suggest that chronic exposure to stress can result in readjustments of central stress-responsive neurotransmitter and neuroendocrine systems normally activated during acute stress. Furthermore, peripheral immune signaling to the central nervous system likely changes over the course of chronic inflammation, potentially resulting in a different HPA axis response. Thus, patterns of cytokine secretion by peripheral blood mononuclear cells differ between patients with early and long-standing RA (*14*). Thus, these physiologic stress response changes in the context of chronic inflammation complicate data interpretation of neuroendocrine responses in inflammatory and autoimmune diseases. It is therefore difficult to establish a causal relationship between HPA axis hyporeactivity and predisposition to inflammatory disease in the context of ongoing established chronic inflammation.

Chronic stress exposure also results in quantitative changes in neuroendocrine activation in response to a second, different stimulus. For example, dampening of the response to acute stimulation occurs in animals with chronic inflammation (*15*). Immobilization stress in rats with adjuvant-induced arthritis will result in increased hypothalamic CRH mRNA expression at 1 week following the injection of adjuvant but not at 2 weeks when the arthritis begins to manifest itself (*16*). This blunted response is not observed when the second acute stressor is inflammatory (*17*). A pre-existing stressor, physical or psychologic, can also dampen the inflammatory response to an immune challenge (*18,19*).

Interactions between the Immune and Neuroendocrine Systems: Bidirectional Communication Pathways

The immune and central nervous systems communicate at multiple levels and reciprocally influence one another (*20–22*). The immune response to tissue injury can be broken down into two steps. Initially, nonspecific inflammation is characterized by vasodilatation with influx of polymorphonuclear white blood cells and their release of a variety of inflammatory mediators. This results in localized swelling, redness, and pain. This may be resolved or lead to a chronic phase of inflammation when the host's immune system mounts a specific attack on foreign antigens. Autoimmunity designates the process by which the immune system targets self-antigens, and can result in a chronic inflammatory process if it goes unchecked by the host's immune regulatory mechanisms. The inflammatory mediators generated during these processes signal the brain through a variety of routes. Cytokines produced systemically and in localized foci of disease such as the synovium in RA play an important role in the pathogenesis of autoimmune diseases (*23*). These cytokines activate neuroendocrine responses by crossing the blood–brain barrier at leaky points (the circumventricular organs), through specific active transport mechanisms (*24*) or by the actions of second messengers such as nitric oxide (*25*). Inflammatory stimuli can also activate the stress response of the central nervous system through afferent peripheral neural signaling. Thus, peritoneal cytokines can cause early rapid activation of the nucleus of the tractus solitarius in the brain stem (*26,27*) via vagal stimulation.

The nervous system in turn regulates the immune system via many routes (*20*). Systemically, the neuroendocrine HPA axis hormonal response modulates both nonspecific and specific immune responses, primarily through the effects of cortisol. Exogenous corticosteroids have long been used in humans as immunosuppressors. It is increasingly recognized that physiologic concentrations of glucocorticoids also regulate immune function (*28*) and function as immunomodulators. At lower concentrations, corticosteroids cause relatively greater suppression of the proinflammatory cytokines tumor necrosis factor-α, and IL-1 (*29,30*) compared to the anti-inflammatory cytokine IL-10 (*31*), and result in a shift in immune response from a T-helper 1 (Th1) cellular-type to a Th2 humoral-type response.

The increased neural sympathetic output resulting from activation of the stress response also likely modulates the immune response. Thus, the sympathetic nervous system plays a role in modulating inflammatory responses through the regional innervation of immune organs such as the spleen, thymus, and lymph nodes (*32*). Sympathetic denervation in animals affects regional inflammation differently depending on the site and mode of the intervention (*33,34*). The natural splenic sympathetic denervation associated with aging may play a role in the immunosuppression observed with aging (*35*). The re-establishment of splenic innervation associatecd with deprenyl administration leads to the reconstitution of splenic immune cell function in aged or denervated animals (*36*).

The nervous system also regulates local acute inflammatory responses through the action of sympathetic postganglionic neurons and their effect on fluid extravasation (*37,38*) and through the release of largely proinflammatory neuropeptides such as CRH, substance P, and vasoactive intestinal polypeptide. They are released at nerve endings or synapses at the site of inflammation or can be produced directly by immune cells. Both peripheral sympathetic noradrenergic nerves and substance P-containing nerves play a role in joint inflammation (*39*). Therefore, some neuropeptides such as CRH can be either pro- or anti-inflammatory (*40*), depending on whether they are localized centrally or peripherally. Central CRH suppresses immune responses through activation of the HPA axis and release of glucocorticoids; peripheral CRH released at nerve terminals is proinflammatory.

Animal Models of Inflammatory Disease, Autoimmunity, and Differential Neuroendocrine Function

A variety of animal models have been used to study autoimmune diseases. The assessment of their stress response and in particular of their HPA axis activation characteristics has been one of the areas of study into disease pathophysiology.

Lewis and Fischer Rats: Inbred Strains at Opposite Ends of the Spectrum of Inflammatory Susceptibility

Lewis (LEW/N) and Fischer (F344/N) rats are major histocompatible inbred rat strains that differ only at one minor histocompatibility locus (the Neu-1 locus). These strains have been used repeatedly to study inflammatory

disorders, as LEW/N rats can develop a variety of autoimmune conditions ranging from uveitis and arthritis to experimental allergic encephalomyelitis (EAE), depending on the antigenic stimulus to which they are exposed (*20*). The neuroendocrine response was initially studied in these rats following their exposure to group A streptococcal cell-wall peptidoglycan polysaccharide (SCW). Following SCW injection, female LEW/N rats develop a progressive erosive arthritis resembling human RA clinically, radiologically, and histologically (*41*). Inflammation-resistant F344/N rats lie at the other end of the inflammatory phenotype spectrum, developing only minimal disease in response to this inflammatory stimulus (*41*). Outbred Harlan Sprague-Dawley rats exhibit intermediate inflammatory susceptibility.

The degree of HPA axis activation response differs significantly between these strains. This difference appears to play an important role in the control of early inflammation, as female athymic LEW/N rats develop the full acute inflammatory response to SCW administration but do not progress to chronic arthritis (*42*). Compared to F344/N rats, LEW/N rats have blunted plasma ACTH and corticosterone responses to a variety of stimuli including SCW, recombinant human IL-1α, the serotonin agonist quipazine, and synthetic rat/human CRH (*41,43*). LEW/N rats also have smaller adrenal glands and larger thymii than F344/N rats. Low-dose exogenous dexamethasone administration significantly decreases the severity of arthritis in LEW/N rats, whereas treatment of F344/N rats with the glucocorticoid receptor antagonist RU486 or the serotonin antagonist LY53857 results in the development of severe inflammatory arthritis. This suggests that LEW/N rat susceptibility to SCW arthritis is related to a defective HPA axis responsiveness to peripheral inflammation and that the resistance of F344/N rats may be due to a robust HPA axis activation pattern.

Surgical and pharmacologic manipulations of the HPA axis in other animal models have provided additional evidence to support a direct cause–effect relationship between endocrine and inflammatory disease traits. Pharmacologic [using the glucocorticoid receptor antagonist RU486, or the serotonin (5-HT2) receptor antagonist LY53857] and surgical (hypophysectomy, adrenalectomy) interruptions of the HPA axis at various levels render animal strains otherwise resistant to inflammation highly susceptible to inflammatory diseases such as EAE (*44*) or arthritis (*41*). Treatment with dexamethasone prevents the development of SCW-induced arthritis (*41*) and partially or completely prevents EAE in response to myelin basic protein (*44*).

Many experiments using this approach have focused on the impact of these interventions on the acute nonspecific phase of inflammation. For example, adrenalectomized rats show a larger and more cellular exudate in response to intrapleural injection of carrageenan, an algae extract used as a nonspecific irritant (*45*). F344/N rats are resistant not only to the development of chronic erosive arthritis but are also less susceptible to acute carrageenan-induced exudative inflammation than LEW/N rats (*46,47*). Similarly, the administration of corticosteroids decreases the acute inflammatory response of LEW/N rats to the level of that observed in the F34/N strain, whereas the administration of RU486 to F344/N rats increases their inflammatory response to levels similar to that of the LEW/N rats (*46*). Surgical manipulations that reconstitute the HPA axis also appropriately modify the peripheral inflammatory response. Thus, transplantation of fetal hypothalamic tissue intracerebroventricularly from Fischer rats into inflammatory-susceptible LEW/N rats decreases subcutaneous carrageenan inflammation in LEW/N rats by over 85% (*48*) while increasing LEW/N hypothalamic CRH expression and plasma corticosterone response to lipopolysaccharide.

LEW/N rats have been used as animal models for other autoimmune diseases. Following the injection of myelin basic protein, these rats develop EAE, an illness that in several ways resembles MS. The administration of exogenous corticosteroids, as in the erosive arthritis model, decreases the intensity of the disease; blockade of corticosteroid action has the opposite effect (*49*).

An example of the use of this rat strain to study putative environmental agents was in the study of L-tryptophan–associated eosinophilia myalgia syndrome (*50*). Treatment of LEW/N rats with case-associated L-tryptophan or one of its derivatives (1,1′-ethylidenebis tryptophan) was associated with the development of an illness with features of fasciitis and perimyositis similar to what has been reported in human pathologic specimens (*51,52*).

Recent linkage studies indicate that the inflammatory susceptibility of these rat strains is polygenic (*53,54*). As suspected, environmental factors play a large role. Thus, the exudate volume phenotype following subcutaneous carrageenan administration in the LEW/N rats has been associated with an environmental variance of 65%.

Murine Lupus Models: HPA Axis and Neuroendocrine Function

Several strains of mice have been used as models for SLE. Although they differ in their disease susceptibility and presentation, they have been found to have an altered HPA axis activation response. When compared to non–lupus-prone mice, NZB, NZW, (NZB/NZW)F_1, and MRL/MP-*lpr* mice have elevated baseline corticosterone levels with a blunted increase following IL-1β injection (*55*). These characteristics are different from those observed in the arthritis-susceptible LEW/N rats discussed above. This is not surprising, as it must be remembered that the diseases collectively referred to as autoimmune in etiology are actually quite diverse in both their clinical presentation and in their pathophysiology. Apart from its defining clinical characteristics and its response to treatment, there is evidence that SLE is characterized by a shifted Th2-type immune response, whereas RA is primarily a Th1-driven process (*56*).

The roles of the hypothalamic–pituitary–gonadal (HPG) axis and prolactin in SLE pathophysiology have also been repeatedly questioned, both in humans and murine models. High estrogen and high prolactin states have repeatedly been associated with increased disease activity and mortality (*57*), whereas treatment with the prolactin-suppressing drug bromocriptine improves outcome (*57,58*). Prolactin has an overall immunostimulatory effect in these mice and appears to potentiate the effect of estrogen on autoantibody production. Estrogen may exert its effects by shifting the lymphocyte response from a Th1- to a Th2-type response (*56,59*).

Avian Models of Autoimmunity

Avian species have provided two important models for human autoimmune diseases. Both show altered HPA axis activation responses. The obese strain chicken spontaneously develops autoimmune thyroiditis and is used as a model for Hashimoto thyroiditis (*60*). Several defects have been identified in this strain at various levels in the HPA axis, and all may contribute to its inflammatory susceptibility. First, these chickens have elevated levels of circulating corticosteroid-binding globulin (*61*), which effectively reduces the available amount of physiologically active corticosterone. This is without any measurable change in GR number and affinity or in circulating corticosterone levels. Second, the animals' corticosterone response to IL-1 injection is significantly blunted. Finally, their thymocytes appear to be resistant to dexamethasone-induced apoptosis. Importantly, dietary iodine content has been found to significantly influence the onset and course of the illness (*62*). Thus, the obese strain chicken represents a good example of the multifactorial etiology of autoimmune diseases. In particular, it illustrates how both specific environmental exposures and coexisting HPA axis defects contribute to the development of pathology.

University of California, Davis (Davis, CA) line 200 White Leghorn chickens

spontaneously develop a systemic fibrotic disease that resembles scleroderma; clinical manifestations include cutaneous fibrosis and polyarthritis, and pathologic examination reveals dermal fibrosis and vaso-occlusive disease (*63*). Additionally, these animals produce a multiplicity of autoantibodies. In response to IL-1 injection, these animals mount a corticosterone response similar to that in normal controls (*64*). However, levels are slower to return to normal. ACTH levels are significantly elevated compared to that in controls, suggesting decreased adrenal responsiveness (*65*).

Implications of These Principles for Susceptibility to Environmentally Induced Autoimmune/Inflammatory Diseases

These experiments illustrate several key points. In addition to supporting the role of the HPA axis and other neuroendocrine factors in regulating the acute nonspecific immune response to antigenic or inflammatory challenge, they suggest that attenuation of early inflammation may significantly reduce the risk of progression to a chronic illness after an exposure. From the point of view of disease pathophysiology, these findings suggest that a hypoactive HPA axis stress response to acute antigenic exposure is one of the many factors predisposing subjects to the development of a chronic inflammatory process. They also raise the issue of whether early corticosteroid treatment may be critical in preventing an acute inflammatory response from evolving into a chronic disease. Furthermore, such studies indicate that a variety of genetic factors, including immune-related and other host response genes, interact with environmental stimuli to produce a final inflammatory disease outcome.

With regard to implications for environmentally induced autoimmune diseases, these studies suggest two mechanisms by which environmental exposures may interact with the neuroendocrine system and result in pathology. First, the premorbid degree of host HPA axis responsiveness, largely genetically or developmentally determined, may be an important variable in governing whether the host goes on to develop chronic autoimmune disease after exposure to an environmental agent with immunogenic potential. Second, exposures to environmental agents with hormonal agonist or antagonist properties could directly interfere with neuroendocrine system function, thereby altering immune response patterns. By disrupting the endocrine response, such agents could indirectly contribute to the development of autoimmune diseases. The study of the hormonal activity of environmental compounds, both man-made and naturally present, has recently gained much attention. Outside of pharmacologic agents, compounds with known glucocorticoid antagonist or antagonist activity are less well studied. However, many chemicals and plants are now known to have estrogenic activity. Whereas most of the focus has been on their peripheral tissue activity, little is known about their central effects on the function of the HPG axis.

Human HPA Axis Activation Response Assessment: Methods and Limitations

Most of the studies of the HPA axis response in humans employ a combination of direct plasma measurements of ACTH and cortisol and dynamic testing of the axis with anterior pituitary stimulation. Plasma hormone measurements at regular intervals over 24 hr can provide a broad quantitative estimate of hormonal secretion as well as insight into potential disturbances in the circadian rhythm of secretion. Direct pituitary stimulation with ovine CRH represents a good test for the assessment of pituitary reserve. It is often performed in conjunction with the infusion of the other main anterior pituitary hormone secretagogues to provide a global assessment of anterior pituitary functional reserves. When interpreting the results in the setting of autoimmune diseases, it is critical to remember the multiplicity of factors that influence the neuroendocrine response. Thus both intrinsic patient characteristics and environmental exposures such as age (*66*), gender (*67*), ethnic background (*68*), weight, psychiatric disorders (*69,70*), acute and chronic disease, chronic pain syndromes, and smoking have effects on HPA axis activation patterns. Of particular relevance in the study of autoimmune diseases is the impact of pharmacologic agents on HPA axis function, as these patients are frequently on several medications.

Neuroendocrine Studies in Rheumatoid Arthritis

Deficient corticosteroid production has repeatedly been questioned as a potential factor in the pathogenesis of RA (*71–73*). Initial findings resulted from simply measuring plasma and urinary cortisol and corticosteroid metabolism products, but more recently a variety of methods have been used to stimulate the HPA axis in order to bring out more subtle defects in the neuroendocrine activation response. Several studies have approached the question by measuring plasma ACTH and cortisol levels at regular intervals (*74,75*). The CRH stimulation test, along with the infusion of the other anterior pituitary stimulatory peptides, has also been used to study neuroendocrine responses in RA patients (*74,76,77*). As previously noted (*78*), overall there appears to be a blunting of the HPA axis response in RA. A recurrent topic of discussion surrounding the data obtained in these studies is the concept of relative adequacy of the HPA axis response. Thus normal circulating ACTH and cortisol levels in the setting of ongoing systemic inflammation do not necessarily indicate an intact HPA axis. Though most results point to intact anterior pituitary and adrenal responses to CRH, it is also possible that the hypothalamus in RA is unable to appropriately react to peripheral inflammation and the stimulatory neural and cytokine signals this generates. Chikanza et al. (*79*) addressed this issue by studying two patient groups—RA and chronic osteomyelitis—and assessed their corticosteroid response to a surgical stressor. Subjects with osteoarthritis and low back pain served as controls. Although the RA patients maintained a circadian rhythm of cortisol secretion, their levels were at the lower end of those observed in controls, and lower than those seen on the osteomyelitis group. Additionally, RA patients failed to show the expected increase in cortisol postoperatively as was observed in the osteomyelitis and osteoarthritis groups. RA appears to be associated to an abnormal hypothalamic response to peripheral inflammation and surgical stress.

Ultimately, the impact of a hypofunctional HPA axis on the inflammatory process depends on the response of the peripheral tissue to circulating glucocorticoids. Schlaghecke et al. (*80*) studied GR affinity and density in patients with active RA who had not been treated with corticosteroids for at least 6 months. Although a decreased number of peripheral lymphocyte GRs was found, this was not associated with any functional difference between the two groups in peripheral lymphocyte cytokine production and proliferation responses in the presence of glucocorticoids (*81*).

These studies do, however, raise questions regarding the potential role of corticosteroid treatment, particularly early on in the disease course. As discussed above, the evidence in animal models suggests that endogenously produced corticosteroids and their exogenous administration are key elements in curtailing acute inflammation and can prevent the development of experimental chronic inflammatory processes (*41*). Although initial enthusiasm for exogenous glucocorticoid treatment in diseases like RA was followed by a more cautious use of the drug, mostly as a result of its side-effect profile, there is now evidence that these agents do have an impact on disease progression (*82*). Of particular interest is the fact that relatively low doses of glucocorticoids may be sufficient to alter the course of disease.

Human studies also support animal findings on the role of the peripheral nervous

system in the immune response. Juvenile RA patients have altered sympathetic system responsiveness as measured using orthostatic stress (*83*). This may be related to an increase in basal sympathetic tone. Additionally, the peripheral mononuclear white blood cells in juvenile RA show reduced response to β-2 adrenergic stimulation, which could potentially result in changes of T-cell and monocyte function. These changes could further contribute to differential inflammatory responses.

Neuroendocrine Studies in Sjögren Syndrome and Systemic Lupus Erythematosus

While numerous studies have been conducted to investigate the HPA axis function in RA patients, similar questions have also been raised in other autoimmune diseases. One of the most prevalent autoimmune diseases that can coexist with RA is Sjögren syndrome. This illness predominantly affects women and is characterized by lymphocytic infiltration of the salivary and lacrimal glands, resulting in clinical symptoms of dry mouth and eyes. Patients are usually antinuclear antibody-positive and may have anti-Ro and/or anti-La autoantibodies along with circulating rheumatoid factor (RF) and hypergammaglobulinemia. The etiology of the disease is unclear. One study of 8 women with Sjögren syndrome showed that along with decreased early-evening basal plasma ACTH and cortisol levels, these patients also had blunted pituitary and adrenal responses to ovine CRH compared to those of controls (*84*). The subjects were similar in menopausal status and were not receiving medications. It remains unclear whether the hypoactivity of the stress response preceded the onset of the disease or was a consequence of ongoing chronic inflammation.

Similar studies have also been performed in patients with SLE. Recently, a controlled study of the HPA axis in seven SLE patients showed significant differences between the two groups in cortisol secretion following insulin-induced hypoglycemia (*85*). The involvement of the HPG axis has also been repeatedly suspected in SLE pathogenesis, in part because women are affected approximately 10 times more often than men. Pregnancy can be associated with worsening of symptoms (*59*). Sex hormones are recognized as affecting the immune system, and estrogen appears to shift the immune response toward a Th2-type response, thereby potentially aggravating the severity of antibody-mediated processes. In males with SLE, the HPG axis functions similarly to that of controls (*86*). Increased peripheral tissue aromatase activity resulting in greater estrogen levels has been suggested as a potential factor aggravating the course of the illness (*87*). The potential negative effects of estrogen on SLE disease activity have raised questions as to the safety of prescribing oral contraceptives and hormonal replacement therapy to women with both active and inactive disease. Additionally, there is increasing evidence that many environmental compounds found in plants, insecticides, and detergents have estrogenic activity and may have effects on diseases such as breast cancer (*88*). It is conceivable that these substances could also impact SLE (*89,90*).

Prolactin has also been the subject of interest in SLE because of its known immunostimulatory properties (*91*). Elevated serum levels have been variably reported in SLE patients (*92*). As in the murine lupus model, higher circulating levels of prolactin have been associated with greater autoantibody titers (*93*). Clinical trials of bromocriptine have had variable success in altering the course of the disease (*94,95*).

Summary

Although our understanding of the pathophysiology of autoimmune diseases remains partial at best, it is clear that their etiology is multifactorial. The neuroendocrine system is a good candidate as one of many host susceptibility factors for autoimmunity because of its role in rapidly responding to a wide variety of environmental exposures and quantitatively and qualitatively modulating the body's response to them. Certainly, studies in animal models support the importance of the stress response in controlling the development of inflammation. The interpretation of studies of the neuroendocrine system in humans with autoimmune disease remains difficult. Indeed, because the study subjects already have ongoing immune activation, a causal relationship between disease susceptibility and abnormal neuroendocrine profiles cannot easily be inferred; it is not entirely clear whether the observed changes precede the onset of illness or are its consequence. Animal models in which premorbid neuroendocrine activity can be studied suggest that such host responses do play a role in inflammatory resistance and susceptibility. Such models also suggest that exposure to chronic stress (in a variety of forms) and/or certain environmental agents can result in adaptation of the organism's stress response and in suboptimal or altered neuroendocrine activation to immunogenic stimuli.

The fact that the neuroendocrine system is key in controlling and dictating the stress response to environmental exposures not only makes it a good candidate as a susceptibility factor for environmentally induced auto immunity but may also account for some of the variability encountered when one attempts to study such illnesses. Indeed, it is critical to keep in mind that multiple variables affect neuroendocrine activation. This is particularly important in the interpretation and design of both animal and human studies examining various aspects of the stress response. Thus, in order to isolate as much as possible the potential effect of the exposure of interest, other environmental factors that may impact neuroendocrine activation must be controlled for in experimental design planning. Ultimately, identification of factors relevant to induction of autoimmune disease will require the determination of multiple genetic factors (both immune and nonimmune related genes), host neuroendocrine and endocrine response systems, and characterization of environmental stimuli that can trigger disease.

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